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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Subject: **METHYL BROMIDE. ID #053201**. Review of Published Study on Chronic Inhalation Exposure of F344 Rats and BDF1 Mice to Methyl Bromide Vapor.

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I. CONCLUSIONS

TB-I has reviewed the submitted article on chronic inhalation toxicity/carcinogenicity of methyl bromide in rats and mice. The results are briefly summarized in the Executive Summary, below and additional details of the study are given below in a brief review (see Discussion).

Executive Summary: In a chronic inhalation toxicity/carcinogenicity study (MRID 44031001; published article), F344 rats were exposed to 0, 4, 20 or 100 ppm methyl bromide vapor and BDF1 mice were exposed to 0, 4, 15 or 64 ppm methyl bromide vapor (50 animals/sex/dose for all groups). Exposures were conducted for 6 hr/day, 5 days/week. Mortality, body weight and microscopic pathology were evaluated.

In rats, body weight of males and females was reportedly decreased compared to controls throughout the study at 100 ppm and from weeks 4 to 30 in males at 20 ppm (values not provided in report). At 100 ppm, necrosis of olfactory epithelium was observed in males (26%) and females (6%) and respiratory metaplasia of olfactory epithelium was increased in males (60% vs 22%, controls).

In mice, body weight of males and females were reportedly decreased throughout the study at 64 ppm (values not provided in report). Atrophy of the granular layer of the cerebellum (slight) was observed at 64 ppm in both males and females (30% vs 0% in controls and other dose groups).

There was no evidence of a treatment-related increase in neoplastic lesions in either rats or mice. Increased incidence of pituitary gland adenoma in male rats at 100 ppm (incidence in controls to high dose, respectively, was 32%, 46%, 38% and 60%) was considered reflective of hormonal imbalance or aging and not a direct carcinogenic effect of methyl bromide.

This study is classified as **Core-supplementary (not upgradable)** and does not satisfy the guideline requirement for 83-1a or 83-2a/b. The study was submitted as additional information and not to satisfy guideline requirements. Definitive conclusions regarding the results of this study cannot be made due to the lack of details in the study report.

II. ACTION REQUESTED

TB-I received for review a published journal article entitled "Two-year Toxicological and Carcinogenesis Studies of Methyl Bromide in F344 Rats and BDF1 Mice - Inhalation Studies" (MRID 44031001), conducted by the Japan Bioassay Laboratory. This study was submitted as additional information on inhalation toxicity of methyl bromide, and not to satisfy guideline requirements for reregistration. Inhalation toxicity studies on methyl bromide in rats and mice have already been submitted (MRID nos. 41213301 and 42418301, rat and 42504101, mouse; see HED Doc. Nos. 007017 and 007845, rat and 011243, mouse for reviews).

III. DISCUSSION

Citation: Gotoh, K., Nishizawa, T., Yamaguchi, T., Kanou, H., Kasai, T., Ohsawa, M., Ohbayashi, H., Aiso, S., Ikawa, N., Yamamoto, S., Noguchi, T., Nagano, K., Enomoto, M., Nozaki, K. and Sakabe, H. "Two-Year Toxicological and Carcinogenesis Studies of Methyl Bromide in F344 Rats and BDF1 Mice - Inhalation Studies." (1994) Environmental and Occupational Chemical Hazards (2). Proceedings of the Second Asia-Pacific Symposium on Environmental and Occupational Health, July 22-24, 1993. MRID 44031001.

Materials and Methods

Test material: Methyl bromide (Sanko Chemical Company, 8 lots stored in cylinders as a compressed gas; purity 99.9%) were stored at room temperature and analyzed by gas chromatography throughout the study. No degradation was observed during the study.

Animals and study design: The supplier of the animals and animal husbandry procedures were not specified in this article. Groups of 50 F344/DuCrj rats/sex/dose group were exposed to 0, 4, 20 or 100 ppm methyl bromide vapor. Groups of 50 Crj:BDF1 mice/sex/dose group were exposed to 0, 4, 16 or 64 ppm methyl bromide vapor. Parameters evaluated during the study included body weight and food consumption. At week 105, animals were sacrificed and given a complete necropsy. Necropsy was also performed on animals that were found dead or sacrificed moribund. All organs were preserved in 10% formalin and evaluated microscopically following hematoxylin and eosin staining of paraffin-embedded sections. Clinical chemistry, hematology and urinalysis parameters were apparently not evaluated, and no mention was made in the report of monitoring of clinical signs.

Data analysis: Body weight and food consumption data were evaluated by a one-tailed Student or Cochran t-test. Neoplastic lesions were analyzed using the chi-squared test. Non-neoplastic lesions were evaluated using Dunnett's multiple comparison using rank from the grade of lesion.

Exposures: Animals were exposed in cages within whole-body exposure chambers for 6 hrs/day, 5 days/week for 104 weeks. Methyl bromide from compressed-gas cylinders was supplied and combined with filtered air to provide the appropriate concentration in each chamber. Chamber concentrations were monitored every 15 minutes using gas chromatography.

Results

Exposure concentrations: Daily concentration variation was plotted graphically. Most weekly variation appeared to be within an acceptable range of target concentration. In both rats and mice, larger than normal variation was observed on 3 occasions during the first 20 weeks of the study.

1. Rat Study

Mortality: Exposure to methyl bromide did not affect survival. At week 104, percent surviving animals, control to high dose respectively, were 68%, 68%, 62% and 66% for males and 84%, 76%, 78% and 82% for females.

Body weight: The report stated that mean body weights of males and females at 100 ppm were lower than controls throughout the study, beginning at week 2, and at 20 ppm were lower than controls between weeks 4 and 30, but did not show body weight values.

Microscopic pathology: Microscopic non-neoplastic and neoplastic lesions are shown in the attached Tables 1 and 2, respectively. Necrosis of olfactory epithelium was observed in high dose males and females and in males, the incidence of respiratory metaplasia of the olfactory epithelium was also increased. In males, inflammation of the olfactory epithelium was observed at higher incidence and severity in treated animals of all dose groups (significant increase at 20 and 100 ppm). Females showed increased inflammation of the olfactory epithelium at 100 ppm.

In males, pituitary gland adenoma was increased at 100 ppm (statistically significant) and in females, adrenal gland pheochromocytoma was increased in all treatment groups. The increased incidence of pituitary gland tumors at high dose was not considered to be a direct result of methyl bromide because it is a common tumor that was probably due to hormonal disturbance or enhanced aging by methyl bromide. Historical control values were not provided for this tumor. The increase in pheochromocytoma in females was not considered treatment-related since no dose-response was observed and values were within the range of historical controls.

2. Mouse Study

Mortality: Exposure to methyl bromide did not affect survival. Percent survival at week 104, control to high dose respectively, was 82%, 72%, 66% and 90% (males) and 64%, 56%, 48% and 70% (females).

Body weight: The report stated that body weight of male mice at 64 ppm was lower than controls throughout the study beginning at week 2 for males and week 1 for females but did not provide values or percent decrease.

Microscopic pathology: Both male and female mice showed increased incidence of atrophy of the granular layer of the cerebellum, classified as slight at 64 ppm.

Although statistically significant increases in malignant lymphoma and hepatocellular adenoma were observed in females at 4 ppm, they were not considered treatment-related because dose-related tumor increases were not observed.

Discussion: Based on the information provided in this report, chronic inhalation exposure to methyl bromide caused an increased incidence of necrosis and respiratory metaplasia of the nasal cavity olfactory epithelium in male rats at 100 ppm and increaseed incidence/severity of inflammation of the nasal cavity at all exposure concentrations. A marginal increase in inflammation of the nasal cavity and necrosis of the olfactory epithelium was observed in female rats at 100 ppm. This is consistent with the previously mentioned

29-month inhalation study in rats in which body weight effects were observed at 90 ppm and respiratory epithelial toxicity (nasal basal cell hyperplasia) was observed at $\geq$3.3 ppm; however, mortality and other effects also were observed at 90 ppm in the earlier study.

In mice, atrophy of the granular layer of the cerebellum was observed in both sexes at 64 ppm. In the NTP mouse 18-month cancer bioassay (see citation above), excessive toxicity, which included cerebellar degeneration and decreased body weight, was seen at 100 ppm and no effects at $\leq$33 ppm.

The apparent lack of treatment-related cancer effects is consistent with the previous studies for both species. However, definitive conclusions regarding the results of this study cannot be made due to lack of sufficient detail in the report.

Table 1 *Non-neoplastic lesions of nasal cavity in rats.*

	Male				Female			
Group (ppm)	Control	4	20	100	Control	4	20	100
Number of examined animals	50	50	50	50	50	50	50	50
Necrosis of olfactory epithelium	0	1	1	13	0	0	0	3
Inflammation	15	26	33	33	16	12	14	26
Respiratory metaplasia of olfactory epithelium	11	17	16	30	3	10	3	5

Table 2 *Neoplastic lesions in rats.*

	Male				Female			
Group (ppm)	Control	4	20	100	Control	4	20	100
Number of examined animals	50	50	50	50	50	50	50	50
Lung								
Bronchiolar-alveolar adenoma	1	4	3	3	0	1	0	1
Thyroid								
Follicular adenocarcinoma	2	0	0	6	0	0	0	0
C-cell adenoma	13	7	11	8	7	7	5	8
Liver								
Hepatocellular adenoma	0	3	0	0	3	2	2	1
Testis								
Interstitial cell tumor	44	43	47	42				
Uterus								
Endometrial stromal polyp					7	8	10	8
Malignant schwannoma					0	3	0	0
Spleen								
Mononuclear cell leukemia	7	8	10	8	7	7	9	6
Pancreas								
Islet cell adenoma	3	6	5	2	0	0	0	1
Mammary gland								
Adenoma	0	0	3	0	8	10	3	2
Subcutis								
Fibroma	6	4	8	4	0	3	1	1
Pituitary gland								
Adenoma	16	23	19	30	35	34	32	26
Adrenal gland								
Pheochromocytoma	15	13	18	16	0	7	5	5
Preputial/clitoral gland								
Adenoma	4	3	4	0	4	1	3	2
Keratoacanthoma	0	1	0	0	1	1	4	0

Table 3 *Non-neoplastic lesions of cerebellum in mice.*

	Male				Female			
Group (ppm)	Control	4	16	64	Control	4	16	64
Number of examined animals	50	50	50	50	50	50	50	49
Atrophy	0	0	0	15	0	0	0	15

Table 4 *Neoplastic lesions in mice.*

	Male				Female			
Group (ppm)	Control	4	16	64	Control	4	16	64
Number of examined animals	50	50	50	50	50	50	50	49
Lung								
Bronchiolar-alveolar adenoma	4	4	2	2	1	0	2	1
Bronchiolar-alveolar carcinoma	9	8	3	7	1	4	1	1
Liver								
Hepatocellular adenoma	15	16	13	14	2	10	1	4
Hepatocellular carcinoma	19	15	9	12	1	1	0	1
Sarcoma	0	3	1	1	0	1	2	0
Ovary								
Cystadenoma					4	5	2	3
Uterus								
Sarcoma					14	12	11	8
Spleen								
Malignant lymphoma	4	5	8	6	7	7	8	9
Hemangioendothelioma	0	0	3	3	0	1	0	0
Lymph node								
Malignant lymphoma	5	1	6	7	6	15	9	12
Subcutis								
Sarcoma	0	2	3	2	0	0	0	0
Pituitary gland								
Adenoma	2	0	0	1	9	11	10	13
Harderian gland								
Adenoma	2	2	2	5	1	3	0	3

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